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Organophosphate Pesticide Exposure and Neurodevelopment in Young Shanghai Children

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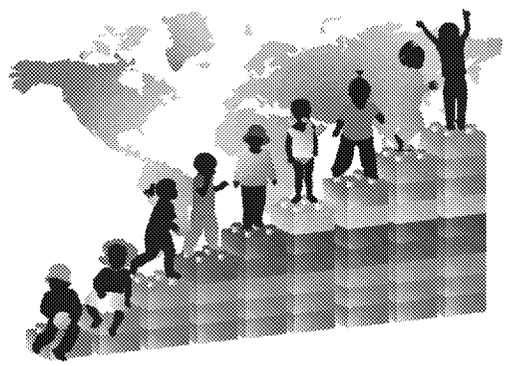
ABSTRACT: A large amount of organophosphate pesticides (OPs) is used throughout China. Animal studies have suggested that even moderate doses are toxic to neurodevelopment, but there are a few studies in humans. We investigated both the urinary levels of OP metabolites in children and their relationship with child neurodevelopment. Participating 301 young children (23−25 months of age) were recruited from two community hospitals in Shanghai between February and October 2008. We measured five nonspecific dialkyl phosphate (DAP) metabolite levels of OPs in the children's urine and examined their association with the children's developmental quotients (DQs) based on the Gesell Developmental Schedules (GDS). The creatinine-adjusted geometric means (GMs) of OP metabolites in urine samples were 11.27 μg/g for DMP; 6.99 μg/g for DMTP; 7.96 μg/g for DEP; 14.19 μg/g for DETP; and 4.55 μg/g for DEDTP. The children had relatively higher levels of OP urinary metabolites compared with those reported in developed countries, no association was found between child urinary levels of OP metabolites and any of the DQ scores. However, our results should be interpreted with caution, and more studies of children living in China are warranted given the relatively high levels of child OP urinary metabolites in Shanghai.



INTRODUCTION

More than 300 000 tons of pesticides are used in agriculture each year throughout China, with organophosphate pesticides (OPs) accounting for more than one-third of these pesticides.[1] OPs are popular because of their broad spectrum of applications, potent toxicity to insects, relatively low costs, and decreased likelihood of pest resistance. Recent studies indicate that pesticide exposures are widespread in some susceptible populations, including pregnant women and children.[2,3] Young children are more susceptible to pesticide exposure due to their unique activity patterns and physiological characteristics. Pound for pound of body weight, young children drink more water, eat more food, and breathe more air than adults. Furthermore, they spend more time playing and crawling on the floor where pesticides may settle and have increased nondietary ingestion through frequent hand-to-mouth and object-to-mouth contacts.[4,5] Young children may also be more susceptible to the potentially neurotoxic effects of pesticides, not only because their organ systems, specifically the brain and central nervous system, are developing rapidly but also because they have lower levels of detoxifying enzymes (paraoxonase or chlorpyrifos-oxonase) that deactivate OPs than adults.[5,6] All these factors indicate that children may be more vulnerable to exposure.

Numerous animal studies have demonstrated that in utero or early exposure to OPs affects neurodevelopment.[7] However, a few epidemiological studies have assessed the neurodevelopment of young children after low-level OP exposure, and these studies have reported inconsistent results.[5,8−10] Marks et al. investigated whether child OP urinary DAP levels were associated with attention in young children, they only found child diethyl phosphate (DE) levels at 5 years were adversely related to attention-related outcomes. Child concurrent total DAP and dimethyl phosphate (DM) levels at 3.5 years and 5 years were unrelated to attention outcomes.[8] Young et al. examined the relationship between in utero and early postnatal OP exposure and neonatal neurobehavior, and they only found that among the >3 day old infants, increasing average prenatal urinary metabolite levels were associated with an increase in

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both the number of abnormal reflexes and the proportion of infants with more than three abnormal reflexes. No detrimental associations were found between postnatal urinary metabolite levels and any of the Brazelton Neonatal Behavioral Assessment Scale clusters for infants ≤3 or >3 days old at assessment.[9] Rauh et al. reported lower mental and psychomotor development scores in 36-month-old children exposed to higher cord-blood levels of chlorpyrifos, a common OP; yet the authors did not observe any association of exposure levels and neurodevelopment at 12 or 24 months.[10]

The hazard of pesticides to children's health has been the subject of great concern globally since the publication of the report "Pesticides in the Diets of Infants and Children" by the National Academy of Sciences (U.S. NAS) in 1993.[11] In developing countries like China, in which OPs are heavily used for agriculture, concerns regarding the adverse health effects of exposure to OPs among child are increasing. This subject area is particularly important because of the OP exposure problems associated with rapid development and a large population.[12] Until now, little information on OP exposure and children's health has been available in China. To our knowledge, this study is the first to investigate the current status of OP exposure in young children living in the metropolitan Shanghai area and to examine the correlation between OP exposure and child health.

We evaluated the relationship of OP urinary metabolite levels with neurodevelopment as measured by the Gesell Developmental Schedules (GDS) and investigated the current status of OP exposure in young Shanghai children, China. We tested the hypothesis that after adjusting for potential confounders, exposure to OPs in young children would be associated with lower DQs in motor, adaptive, language, and social areas.

MATERIALS AND METHODS

Participants and Recruitment. From February through October 2008, we recruited young children, 2 years of age, to participate in this study from the departments of child and adolescent healthcare of two community hospitals in Shanghai. The participants were healthy children who were attending the departments for routine physical check-ups. Children considered eligible for the study were between 23 and 25 months of age and reported no intrauterine distress, pathologic jaundice, intrauterine infection, intracranial infection, or congenital disease. Participating children were generally in good health without current illness (cold or fever), and able to complete the Gesell Developmental Schedules (GDS). A total of 310 children met the eligibility criteria, among whom 301 parents provided consent for their children to take part in this study (response rate 97.1%). All parents signed the consent form approved by the Shanghai Jiao Tong University School of Medicine Institutional Review Board.

Maternal Interviews and Assessments. A trained interviewer administered a 30 min questionnaire to the mothers. The questionnaire included the following: demographic information and exposure characteristics such as child's surname, name, sex, age, illnesses, and hospitalizations, address, telephone number, and type of residence (location, duration, and ownership of residence); environmental exposures (nearby field, indoor insecticide use, para-occupational exposures); child characteristics (dietary habits, hand-to-mouth contact, passive smoking); and maternal characteristics (any smoking or alcohol use during pregnancy, employment). Other relevant information such as date of birth, gestational age, head circumference at birth, weight, and height were derived from child medical records. Socioeconomic information related to household income and parents' education level was also collected. If the questionnaire was incomplete, the mothers were contacted by telephone to obtain the missing information.

Urine Collection and Urinalysis. Urine samples were collected from each participant at intervals throughout the day when the study assessments were completed. Specimens were aliquoted into precleaned glass containers with Teflon-lined caps, bar coded, and stored at cold temperatures (2−4 °C) or frozen until shipment. Samples were shipped overnight on dry ice to the CDC (Shanghai, China) and stored at −70 °C until analysis. Urine samples were analyzed for DAP metabolites of OPs using the method of gas chromatography with flame photometric detection (GC-FPD). Five analytes were measured in each sample: DMP, DMTP, DEP, DETP, and DEDTP. To provide an overall assessment of precision, accuracy and overall reliability of the method, we analyzed quality control (QC) samples along with the collected samples. QC samples were prepared as blank samples and inserted blindly among the study samples.

The limit of detection (LOD) for each of the metabolites was calculated from the instrument response factor corresponding to a concentration having a peak area three times of the baseline noise (blank signal). The specific LODs for the five metabolites were 2.0 μg/L for DMP and 1.0 μg/L for DMTP, DEP, DETP, and DEDTP. Individual metabolite levels below the LOD were assigned a value equal to the LOD divided by the square root of two,[13] and this value was included in each sum.

Summed molar concentrations of two dimethyl metabolites (DMP, DMTP) and the three diethyl metabolites (DEP, DETP, DEDTP) were calculated to provide summary measures of exposure that were less affected by results below the LOD for individual metabolites. The converted formula for each metabolite from its untransformed concentration (μg/L) to the corresponding molar concentration (nmol/L) was described elsewhere.[14]

Metabolite concentrations were adjusted using creatinine concentrations to correct for variable urine dilutions in the spot urine samples. Creatinine concentrations in urine were determined using a commercially available diagnostic enzyme method (Vitros CREA slides; Ortho Clinical Diagnostics, Raritan, NJ).

Neurodevelopment Measures and the Gesell Developmental Schedules (GDS). The GDS was designed to provide a neurologic and intellectual evaluation of the infant or child at the time of testing and to facilitate decision-making regarding services needed by the infant or child. In the present study, the GDS was selected for comparability with other studies done in the Chinese population because it has been adopted by the Chinese Pediatric Association, has been validated against a Chinese reference population,[15] and is widely used for assessing child development in China and other countries.[16,17] Children in the cohort, who were 2 years of age, were administered the version of the GDS for 0- to 3-year-old children revised by the Beijing Mental Development Cooperative Group and adapted to the Chinese population.[18,19]

The items in the scale are grouped into four main categories of functioning: motor behavior, including locomotion, reaching, balance, comprehension, drawing, and hand control; adaptive behavior, including hand-eye coordination, imitation, object recovery, comprehension, discriminative performance, perception, completion, and number conception; language behavior,

Table 1. Demographic and Exposure Characteristics for 301 Young Children Aged 23-25 Months in Shanghai, China, 2008

demographic and exposure characteristics	N	%
Para-Occupational Exposure		
mother does farm work	0	0.0
father does farm work	1	0.0
Residential Exposure		
location of dwelling		
urban area	297	98.7
suburban area	4	1.3
duration of dwelling		
< 3 years	88	29.2
3–5 years	90	29.9
5–10 years	53	17.6
> 10 years	70	23.3
ownership of dwelling		
own	172	57.1
rent	83	27.6
other	46	15.3
indoor insecticide use in last half year		
yes	125	41.5
no	176	58.5
Environmental Exposure		
nearby field		
adjacent to agricultural field	4	1.3
adjacent to green park	170	56.5
not adjacent	127	42.2
passive smoking		
never	181	60.1
occasional	80	26.6
often	40	13.3
fruit consumed weekly		
never	4	1.3
1–3 times	20	6.6
4–6 times	31	10.3
daily	246	81.7
vegetables consumed weekly		
never	4	1.3
1–3 times	12	4.0
4–6 times	20	6.6
daily	265	88.0
Environmental Exposure		
fruit juice consumed weekly		
never	144	47.8
1–3 times	71	23.6
4–6 times	24	8.0
daily	62	20.6
Child and Mother Characteristics		
child sex		
female	139	46.2
male	162	53.8
hand-to-mouth contact		
never	149	49.5
occasional	8	2.7
often	144	47.8
mother's level of education		
elementary school	31	10.3
high school	62	20.6
greater than high school or college	208	69.1
mother's employment		
none	69	22.9
part time	87	29.0
full time	145	48.2
alcohol use during pregnancy		
yes	3	1.0
no	298	99.0
smoking during pregnancy		
yes	2	0.7
lived with smoker	38	12.6
no	261	86.7
father's level of education		
elementary school	20	6.6
high school	64	21.3
greater than high school or college	217	72.1
household monthly salary (RMB)		
< 2000	12	4.0
2000–5000	89	29.6
5000–10 000	112	37.2
>10 000	88	29.2

assessed by means of vocabulary, word comprehension, conversation, and word production; and personal and social behavior, including reactions to people, personal habits, initiative and independence, play responses, and acquired information. Each child was assigned a developmental quotient (DQ) in each of the four specific domains: motor, adaptive, language, and social. The standardized mean (±SD) of the DQ is 100 ± 15. A score of 84 is the cutoff point for differentiating normal development from developmental delay. Scores of 70–84 indicate moderate delay, and scores of <70 indicate severe delay.[19]

Testing was conducted by a trained pediatrician to maximize both the reliability of the assessment and the validity of the interpretation. The tester completed a 2-week course and 1-year clinical practice at Shanghai Jiao Tong University and passed standardized exams to become certified.

Data Analysis. SPSS software (SPSS Inc., Chicago, IL) was used for all analyses. Initial descriptive statistics were calculated for the individual OP metabolites, summed dimethyl and diethyl metabolites and DQ scores. To ensure that creatinine levels did not affect the outcomes, we calculated the OP urinary metabolite levels with adjustment for creatinine. Nonspecific DAP metabolites (nmol/g creatinine) were summed and transformed to the $\log_{10}$ scale. To assess the relationship between child urinary metabolite levels and GDS performance, we constructed separate regression models for each of the four areas. We included the same covariates in all regression models. Covariates were selected for these analyses if they were related to neurodevelopment in the literature and were significantly associated ($p < 0.10$) with 2 or more GDS DQs (outcomes) (i.e., child sex, maternal education level and household income). All regression analyses were run using log-transformed creatinine-adjusted metabolites.

RESULTS

The demographic and exposure characteristics of the study sample are shown in Table 1. Data from 301 healthy young children were analyzed in the present study. Their mean age was 24.15 months (SD = 0.88), mean body weight was 12.84 kg (SD = 1.46), and mean body height was 88.72 cm (SD = 6.41). Overall, 53.8% of the sample was male. Nearly all of the children (98.7%) came from urban areas, and almost three in five (n = 174, 57.8%) lived adjacent to a green space or

Table 2. Detection Frequency, Creatinine Unadjusted and Adjusted Geometric Mean, Range and Percentile for 301 Young Children Aged 23-25 Months in Shanghai, China, 2008

		not adjusted for creatinine (μg/L)						creatinine adjusted (μg/g)					
				percentile of distribution						percentile of distribution			
metabolites	detection no. (%)	GM	range	25th	50th	75th	95th	GM	range	25th	50th	75th	95th
DMP	126 (41.9)	2.52	<LOD −186.99	<LOD	<LOD	3.41	30.20	11.27	1.53−729.27	4.33	9.85	24.02	125.69
DMTP	110 (36.5)	1.56	<LOD −80.81	<LOD	<LOD	1.63	10.31	6.99	1.08−481.50	3.09	5.98	13.12	58.65
DEP	216 (71.8)	1.78	<LOD −32.19	<LOD	1.23	2.89	7.73	7.96	1.14−170.96	3.84	7.44	16.36	54.73
DETP	208 (69.1)	3.18	<LOD −55.40	<LOD	2.93	7.26	20.45	14.19	1.10−980.58	5.30	12.45	37.15	128.97
DEDTP	8 (2.7)	NC	<LOD −3.80	<LOD	<LOD	<LOD	<LOD	4.55	1.08−73.14	2.49	4.45	7.70	18.36

agricultural field. More than 80% consumed fresh fruit and vegetables daily; however, only 20% drank fruit juice daily. Roughly 10% often had passive smoking exposure, and most (60.1%) were not exposured to smoking. Nearly half of these children displayed extensive hand-to-mouth contact. The majority of the mothers (89.7%) and fathers (93.4%) had completed high school or college. Two-thirds of the children lived in households with a monthly salary greater than RMB 5000. Almost none of the mothers consumed alcohol regularly during pregnancy, and few smoked or lived with a smoker.

OP urinary metabolite levels of the study sample, both unadjusted and adjusted for creatinine, are summarized in Table 2. The percentage of samples in which the OP metabolites were more than the LOD ranged from a low of 2.7% for DEDTP to a high of 71.8% for DEP. The maximum value without creatinine adjustment was 186.99 μg/L for DMP and 80.81 μg/L for DMTP; the maximum value with creatinine adjustment was 980.58 μg/g for DETP and 729.27 μg/g for DMP. The GM values without creatinine adjustment for DMP, DMTP, DEP and DETP levels were 2.52, 1.56, 1.78, and 3.18 μg/L, respectively; the GM for DEDTP levels was not calculated because of low detection frequency. The creatinine-adjusted GMs for DMP, DMTP, DEP, DETP, and DEDTP levels were 11.27, 6.99, 7.96, 14.19, and 4.55 μg/g, respectively.

The distribution of Gesell Development Schedules (GDS) DQ scores of the study sample is shown in Table 3. The arithmetic means for motor, adaptive, language and social scores were 103.07 (SD = 7.59), 107.03 (SD = 11.87), 104.27 (SD = 16.22), and 96.11 (SD = 7.34), respectively, and the frequency of developmental delay ranged from 0.3% (motor) to 6.3% (language).

Table 3. Distribution of GDS DQ Scores for 301 Young Children aged 23−25 Months in Shanghai, China, 2008.[a]

	mean ± SD (range)	normal (*n* (%))	developmental delay (*n* (%))
motor area	103.07 ± 7.59 (83−125)	300 (99.7)	1 (0.3)
adaptive area	107.03 ± 11.87 (79−136)	297 (98.7)	4 (1.3)
language area	104.27 ± 16.22 (66−146)	282 (93.7)	19 (6.3)
social area	96.11 ± 7.34 (71−133)	293 (97.3)	8 (2.7)

[a]Normal, > 84; developmental delay, ≤ 84.

Table 4 presents adjusted regression coefficients and 95% confidence intervals, based on the entire sample, for each of the four area scores regressed separately on total DAP, dimethyl, and diethyl phosphate metabolite levels measured. We did not observe any statistically significant associations between metabolite levels and any of the DQ scores.

DISCUSSION

Organophosphate Metabolite Levels in Young Children. The current status of OP exposure in children is concerning, and this study is the first to provide urinary DAP levels for young children, recruited from two community hospitals in Shanghai. As shown in Table 5, we found that the young children in Shanghai had higher levels of diethyl metabolites (DEP, DETP, and DEDTP) and equivalent levels of dimethyl metabolites (DMP, and DMTP) comparing to the reference data in GerES IV 2001−2002 or a relevant Italian study.[20−22] For example, the GM and 50th percentile of DEP levels for German children were 2.6 and 3.0 μg/g creatinine, and the corresponding measures in this study were 8.0 and 7.4 μg/g creatinine, whereas the GM and 50th percentile of DMP levels for German children were 10.7 and 10.7 μg/g creatinine, our corresponding findings were 11.3 and 9.9 μg/g creatinine. We also found that all the DAP levels (DMP, DMTP, DEP, DETP, and DEDTP) of young Shanghai children were significantly higher than those of children age 6−11 years in the NHANES 2003−2004 study.[23] For example, the GMs of DAP levels ranged from less than the LOD to 3.4 μg/g creatinine (for DMTP) in children 6−11 years of age in the U.S. general population, whereas the GMs of DAP levels in our sample ranged from 4.6 (DEDTP) to 14.2 (DETP) μg/g creatinine.

The differences in DAP levels between our study and other reference values reported in the American, German and Italian data may be caused by a variety of factors. First and most importantly, people in China might have high OP exposure levels because of heavy use and high residue in the common raw food supply. OPs are widely used for agriculture in China, with an annual utilization of more than 100 000 tons (approximately 220 million pounds).[1] However, approximately 60 million pounds of OPs were applied to U.S. crops annually, and nonagricultural uses account for an additional 17 million pounds.[24] A recent study in China found that among the 2520 milled rice samples examined, 235 (9.3%) contained detectable residues of at least one of the seven target OPs (chlorpyrifos, dichlorvos, omethoate, methamidophos, parathion-methyl, parathion, and triazophos), with levels ranging from 0.011 to 1.756 mg/kg, and 165 samples (6.5%) exceeded the national maximum residue limits (MRLs) (0.05 mg/kg for triazophos and omethoate, 0.1 mg/kg for the

Table 4. Adjusted[a] Coefficients (β) (95% CIs) in Points on the Motor, Adaptive, Language, And Social Areas of the Gesell Developmental Schedules for a Log_{10} Unit Increase in OP Urinary Metabolites

	dialkylphosphate metabolites[b] (nmol/g creatinine)					
	total dialkyl phosphates		dimethyl phosphates		diethyl phosphates	
	β (95% CI[c])	p-value	β (95% CI[c])	p-value	β (95% CI[c])	p-value
motor area	0.30 (−1.40, 1.99)	0.73	−1.25 (−2.98, 0.47)	0.15	0.32 (−1.37, 2.01)	0.71
adaptive area	1.71 (−1.15, 4.57)	0.24	2.53 (−0.05, 5.10)	0.06	−0.41 (−3.22, 2.39)	0.77
language area	2.79 (−1.01, 6.60)	0.15	2.83 (−0.60, 6.26)	0.11	−0.29 (−4.02, 3.44)	0.88
social area	−0.66 (−2.12, 0.79)	0.37	−0.48 (−1.93, 0.97)	0.51	−0.93 (−2.40, 0.54)	0.22

[a]Model included child sex, maternal education level, and household income as covariates. [b]Urinary metabolite levels are adjusted for urinary creatinine concentration. [c]CI, confidence interval.

other five OPs listed above).[25] It is worth noting that each of the target OPs with residue levels higher than the national safety standard for milled rice was found in milled rice samples.[26] A study of pesticide residue in domestic processed rice was conducted by the U.S. Food and Drug Administration (FDA) in 1993−1994 and showed that levels of most pesticide residues found in processed rice were generally well below U.S. standards, and few violative residues (1.3%) were found.[27]

Second, our subjects were considerably younger than those in other studies. Young children eat more fresh produce and drink more water, milk, or fruit juice than do school-age children or adolescents in proportion to body weight. Other types of exposure may be greater for young children; they may be more exposed to pesticide residues in house because they play on the floor and put things in their mouths (i.e., oral nondietary and cutaneous exposure).[4,5] In addition, a young child is likely to have a lower level of creatinine than a school-age child or adolescent; therefore, a DAP level in the young child may be overcorrected when adjusting for creatinine, producing a DAP level that is falsely elevated compared with that of an older child with a similar exposure and uptake profile.[28]

Although young Shanghai children have higher levels of OP urinary metabolites, the detection frequencies of OP urinary metabolites are generally lower than those in some American, German, or Italian studies.[20,21,28] The discordance of detection frequencies among these studies may be attributed to the differences in experimental protocols such as LODs or study populations. Our LODs were higher than those in the American study,[28] but similar to those in German and Italian studies.[20,21] Furthermore, we repeated regression models among the children with urinary DAP metabolite levels higher than LODs, no significant association was found between OP urinary metabolite levels and DQ scores (data not shown). Thus, we considered that the relatively high LODs might not have influenced the essentially findings of this study.

We also found that the detection frequencies of OP urinary metabolites in children in our sample ranged from a low of 2.7% for DEDTP to a high of 71.8% for DEP. Coye et al. reported that the metabolites of DMP and DEP are directly associated with exposure to OPs, whereas metabolites of DMDTP and DEDTP are less directly associated with exposure because they break down rapidly to the corresponding monosulfates (DMTP and DETP) and phosphates (DMP and DEP).[29] This may explain the low detection frequency of the disulfate metabolite (DEDTP) in the urine samples in this study (Table 5).

Effects of Organophosphate Pesticide Exposure on Neurodevelopment. The present study not only investigated the child OP urinary metabolite levels but also analyzed the correlation between OP exposure and children's neurodevelopment. Regression analyses suggested that OP exposure in children, as measured by total DAP, dimethyl phosphate and diethyl phosphate metabolites, may not be negatively associated with developmental quotients (DQs) in motor, adaptive, language, and social scores based on the Gesell Developmental Schedules (GDS) (Table 4).

A few previous studies have examined low-level chronic exposure to OPs and children's neurodevelopment, and also they have reported inconsistent results.[5,8−10] Therefore, it is challenging to conduct studies to evaluate the effects of OP exposure on neurodevelopmental outcome. For example, in a recently published, large longitudinal study from the agricultural Salinas Valley of California, Eskenazi et al. examined the relationship between prenatal and child OP urinary metabolite levels and the children's performance at 6, 12, and 24 months of age according to the Bayley Scales of Infant Development (Mental Development (MDI) and Psychomotor Development (PDI) Indices). They found adverse associations between prenatal DAP exposure and MDI at 24 months of age, but children's concurrent DAP levels were unexpectedly positively associated with MDI scores. No associations were observed between prenatal or child DAP exposure and MDI at 6 or 12 months of age or with PDI at any of the three time points.[5] Our study also did not observe significant associations between metabolite levels and any of the DQ scores in the motor, adaptive, language, and social areas.

To our knowledge, this study is the first in China to examine possible adverse effects of child OP exposure on children's neurodevelopment. However, our study also has several limitations. First, although measurement of DAP metabolites is the most current method to characterize and integrate exposure to multiple OPs that originate from different sources, urinary metabolite levels may reflect exposure not only to OP parent compounds, but also to the potentially nontoxic preformed metabolites in the environment.[30] Second, as in most studies on the effects of pesticide exposure, we measured OP urinary metabolites at a single time point only. We are limited in our ability to know what the average cumulative dose from different sources was and to what extent these measurements accurately reflected exposure throughout the entire critical period of neurodevelopment.[5] In addition, our study is also limited by the small sample size and we did not use tests that focus on specific neurodevelopmental domains which might more readily detect the effects of OPs.

In summary, OP metabolite levels were not found to be associated with DQ scores in young children. However, our results should be interpreted with caution given the relatively high levels of child OP urinary metabolites in Shanghai. A large

Table 5. Between-Study Comparison of DMP, DMTP, DEP, DETP and DEDTP Urinary Metabolite Levels in Children[a]

						percentile of distribution			
metabolites	study/author	country	sample size/age	detection frequency (%)	GM	25th	50th	75th	95th
DMP									
	Shanghai, 2008	China	n = 301, 23–25 months	41.9	11.3	4.3	9.9	24.0	125.7
	NHANES, 2003–2004[23]	U.S.	n = 310, 6 - 11 years	NA	NC	<LOD	<LOD	6.9	19.6
	GerES IV 2001–2002[20]	Germany	n = 363, 2 - 17 years	79.0	10.7	NA	10.7	NA	95.8
	Aprea et al. (2000)[21]	Italy	n = 195, 6 - 7 years	96.0	14.6	8.2	13.8	28.0	NA
DMTP									
	Shanghai, 2008	China	n = 301, 23–25 months	36.5	7.0	3.1	6.0	13.1	58.7
	NHANES, 2003–2004[23]	U.S.	n = 310, 6 - 11 years	NA	3.4	NA	3.4	7.9	36.1
	GerES IV 2001–2002[20]	Germany	n = 363, 2 - 17 years	90.0	6.5	NA	6.3	NA	109.0
	Aprea et al. (2000)[21]	Italy	n = 195, 6 - 7 years	94.0	14.8	8.2	14.1	27.0	NA
DEP									
	Shanghai, 2008	China	n = 301, 23–25 months	71.8	8.0	3.8	7.4	16.4	54.7
	NHANES, 2003–2004[23]	U.S.	n = 308, 6 - 11 years	NA	NC	<LOD	<LOD	6.1	16.1
	GerES IV 2001–2002[20]	Germany	n = 363, 2 - 17 years	81.0	2.6	NA	3.0	NA	14.1
	Aprea et al. (2000)[21]	Italy	n = 195, 6 - 7 years	75.0	5.1	2.7	5.5	9.8	NA
DETP									
	Shanghai, 2008	China	n = 301, 23–25 months	69.1	14.2	5.3	12.5	37.2	129.0
	NHANES, 2003–2004[23]	U.S.	n = 296, 6 - 11 years	NA	NC	<LOD	<LOD	0.9	2.7
	GerES IV 2001–2002[20]	Germany	n = 363, 2 - 17 years	45.0	0.9	NA	NA	NA	NA
	Aprea et al. (2000)[21]	Italy	n = 195, 6 - 7 years	48.0	2.7	1.1	2.5	5.7	NA
DEDTP									
	Shanghai, 2008	China	n = 301, 23–25 months	2.7	4.6	2.5	4.5	7.7	18.4
	NHANES, 2003–2004[23]	U.S.	n = 310, 6 - 11 years	NA	NC	<LOD	<LOD	<LOD	0.5
	GerES IV 2001–2002[20]	Germany	n = 363, 2 - 17 years	<1	NA	NA	NA	NA	NA
	Aprea et al. (2000)[21]	Italy	n = 195, 6 - 7 years	12.0	1.4	0.86	1.1	2.1	NA

[a]NC, not calculated because proportion of results below the LOD was too high to provide reliable result; NA, not applicable; Unit is μg/g creatinine (creatinine-adjusted levels) for individual metabolites.

longitudinal study with repeated measurement of exposure levels in urine samples is needed to examine the relationship between OP exposure and child neurodevelopment.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DMP	dimethylphosphate
DMTP	dimethylthiophosphate
DMDTP	dimethyldithiophosphate
DEP	diethylphosphate
DETP	diethylthiophosphate
DEDTP	diethyldithiophosphate
DM	dimethyl phosphate
DE	diethyl phosphate
DAP	dialkyl phosphate
GM	geometric mean
OP	organophosphate pesticide
DQ	developmental quotient
GDS	Gesell Developmental Schedules
LOD	limit of detection

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